LETTER TO THE EDITOR

# Imatinib mesylate in the management of chemotherapy-induced pulmonary toxicity: a double-edged sword

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With the introduction of imatinib mesylate (IM), the first *BCR-ABL1* tyrosine kinase inhibitor (TKI), the outcome of patients with chronic myeloid leukemia (CML) improved dramatically. Besides the inhibition of *BCR-ABL1*, TKIs may target other kinases, which is generally called the "off-target" effects. Adverse events (AEs) are off-target effects that sometimes can be problematic for both the patient and the physician [1].

Pulmonary toxicities are well-known AEs of chemotherapy and immunotherapy, which sometimes are hard to manage. I have read the paper with great interest by Langberg and colleagues [2], who shared their experiences with the use of IM in life-threatening steroid-refractory chemotherapy-induced pulmonary toxicity among four patients with testicular cancer. The authors clearly showed that all patients responded well to the TKI therapy; however, I still have some concerns about the use of IM in patients with chemotherapy-induced pulmonary toxicity.

As the authors stated, IM was previously used in patients with cancer experiencing chemotherapy-induced pneumonitis especially due to the use of bleomycin [3,4]. We know that IM can be used in patients with scleroderma-like chronic graft-versus-host disease (cGvHD) after allogeneic hematopoietic stem-cell transplantation (allo-HSCT) [5]. Both platelet-derived growth factor receptor (PDGFR) and transforming growth factor β pathways are involved in the pathogenesis of this complication, and it is known that IM is a potent inhibitor of PDGFR as an off-target effect.

On the other hand, although not frequent, it was shown that IM can also induce pneumonitis in patients with CML [6–8]. In the study by Ohnishi et al. [9], among 5500 patients receiving IM, there were 27 cases of interstitial lung disease. The median period to develop interstitial pneumonitis from the start of IM was 49 d and the median daily dose of the drug at the time of the diagnosis was 400 mg. However, in the study of Ohnishi et al. [9], no significant correlation was observed between the development of pulmonary complication and the dose or the duration of IM. In addition to that, in a patient with idiopathic pulmonary fibrosis (IPF), severe dyspnea on exertion developed after receiving IM for CML [10]. Discontinuation of IM and methylprednisolone pulse therapy followed by oral prednisolone resulted in improvement of both symptoms and radiographic findings in this case with IM-induced pneumonitis together with underlying IPF.

The pathogenesis of IM-induced interstitial pneumonitis may include the inhibition of PDGF tyrosine kinase, which is a target for IM [11,12], as its therapeutic action is thought to occur partly via the inhibition of the same tyrosine kinase in patients with chemotherapy-induced pulmonary toxicity as "a double-edged sword."

The dose of IM in patients experiencing IM-induced pneumonitis is usually 400 mg daily, whereas the dose administered in the study of Langberg et al. [2] was a lower dose (300 mg/d or less) as stated before [3], and also the dose can be as low as 100–200 mg daily in patients with cGvHD following allo-HSCT [5]. Generally, there is a dose–response relationship for drug-induced pneumonitis, and the optimal dose of IM for treating chemotherapy-induced pneumonitis is unknown. Most probably the daily dose of IM in the management of chemotherapy-induced pulmonary toxicity should be lower than that of used in patients with CML resulting in IM-induced pneumonitis.

As to conclude, IM can be a treatment option in patients with severe steroid-refractory chemotherapy-induced pulmonary toxicity as shown by Langberg et al. [2]; however, one should never forget that the drug itself can also cause pneumonitis, which hypothetically may worsen the clinical picture.

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LETTER TO THE EDITOR

# Pazopanib in relapsed osteosarcoma patients: report on 15 cases

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Osteosarcoma is a rare bone tumor that occurs in young adults with a subsequent peak in the fifth decade. Neoadjuvant and adjuvant chemotherapy and surgery cure approximately 60% of patients with localized osteosarcoma [1]. Metastases occur in about 30–40% of patients, and are mainly localized in the lungs [1,2]. Survival in the metastatic setting is 20–25% at 5 years [1–3], and depends on metastatic site (lung versus other sites), number of metastases and disease-free interval [3,4]. Surgery is the preferred therapy if the metastases are resectable, and chemotherapy is an option when surgery is not feasible. The drugs used at relapse are usually gemcitabine and docetaxel [response rates (RR) 15–30%] [5–7], high-dose ifosfamide [RR 30–40%] [8,9] or etoposide.

As for many other orphan diseases, there is a limited development of new drugs for osteosarcoma, and new therapeutic principles often rely on repurposing of drugs originally developed for other indications. Pazopanib is an orally administered multi-target receptor tyrosine kinase inhibitor (TKI) approved for soft tissue sarcoma and renal cancer. It is an inhibitor of several kinases, including VEGF, PDGF, and cKIT. Its toxicity profile is quite favorable, but still about two-thirds of patients have to reduce dose for toxicity (e.g., hypertension, hypothyroidism, and hand–foot syndrome) [10].

So far only case reports have been published on pazopanib in advanced osteosarcoma. A Danish study [11] reported three patients with clinical benefit, and a Japanese report [12] demonstrated one out of three cases with prolonged response. There are also ongoing clinical trials and unreported completed trials with different TKIs where osteosarcoma patients are eligible, including pazopanib (NCT01759303), lenvatinib (NCT02432274), apatinib (NCT02711007), and regorafenib (NCT02389244).

Here, we report the results from two large sarcoma reference centers of pazopanib treatment in metastatic osteosarcoma patients after failure of conventional chemotherapy.

## Material and methods

All patients with metastatic osteosarcoma treated with pazopanib at Rizzoli Orthopedic Inst, Bologna (Italy) and at Oslo University Hospital (Norway) were included. In Bologna, a compassionate use permit was obtained from the hospital

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